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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/493,353	01/28/2000	Jeffrey M. Linnen	CDS-211	2146

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/493,353	LINNEN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/1/02; April 22, 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-6,8-12,27-32,34-38,43-46,49,50,54-57,60 and 61* is/are allowed.

6)☒ Claim(s) *7, 13-26, 33, 39-42, 47-48, 51-53, 58-59, 62-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed April 22, 2002; July 1, 2002. Currently, claims 1-64 are pending. All arguments and the declaration by Kevin M. Gorman, filed April 22, 2002 have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 22, 2002 has been entered.

3. This action contains new grounds of rejection necessitated by amendment.

Priority

4. This application claims priority to 60/118,497, filed February 3, 1999.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991).

Han et al. (herein referred to as Han) teaches the sequence of 341 base pairs from the 5' untranslated region (UTR) of HCV and alignment of this sequence from several different HCV isolates. Han teaches extracting the plasma from HCV-positive or negative blood donors. RNA was isolated and converted into single-stranded cDNA by reverse trancriptase using the appropriate cDNA primer (pg 1711, col 2). Han teaches primers for the PCR amplification of 5' UTR and means of cloning these PCR products (pg. 1711, col. 2, and Figure 2). The PCR products were analyzed by southern blot hybridization using a labeled oligonucleotide probe (pg 1711, col 2). Han teaches that when the sequence of the 5' UTR is compared among isolates, there is a high degree of sequence homology and that the sequence mismatches that are present are clustered in 5 positions, as taught in Figure 2 (see also pg. 1713, para 1). Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4). Han teaches Primer 51 was used to primer cDNA synthesis on HCV RNA extracted from plasma (pg 1712, col. 1). Primer 51 is located from position 268-251 (Figure 2). Moreover, Han teaches primers 52, 11, 95 and probes 89 and 90a. Primer 95 overlaps SEQ ID NO: 1, CAGAAAGCGTCTAG are in common.

Han does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent functional equivalents of Han 95, 89, 52, 51 primers, in which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Han to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Han. Since Han provides an alignment of several isolates which show conserved regions between the isolates, and delineates the ORFs, the ordinary artisan would have been motivated to have designed primers which amplify various regions of interest from the 5' UTR region. Specifically, the skilled artisan would have picked SEQ ID NO: 1 and 4 to have amplified the ORF2 and would have chosen SEQ ID NO: 2 and 7, SEQ ID NO: 3 and 5 or SEQ ID NO: 3 and 6 which flank ORF3. Furthermore, the skilled artisan would have chosen SEQ ID NO: 11, 12 or 13 for

probing the detection of HCV. The ordinary artisan would have been motivated to amplify the 5' UTR region of HCV since Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose. Thus, any primers which amplify the 5' UTR region and any probes within the 5' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The rejection is not applicable to the primer pair of SEQ ID NO: 1 and 4 and the primer pair of SEQ ID NO: 2 and 7, since the specification provides unexpected results with respect to these primer pairs. The rejection was applicable to primer pairs of SEQ ID NO: 3, 5, 6 for 5'NCR region of HCV and 8 and 9 for the 3' NCR region of HCV.

Moreover, MPEP 716.02(d), provides that the unexpected Results must be Commensurate in Scope With Claimed Invention. The claims drawn to single oligonucleotides, Claims 40-42, are not encompassed by the unexpected results of the specification, nor the asserted unexpected results of the declaration. The unexpected results are drawn to pairs of primers. Thus, single oligonucleotides are not commensurate in scope with the unexpected results. Han has taught four primers which amplify 5' UTR and two probes for this region. Han teaches Primer 51 was used to prime cDNA synthesis on HCV RNA extracted from plasma (pg 1712, col. 1). Primer 51 is located from position 268-251 (Figure 2). SEQ ID NO: 12 overlaps primer 51.

Moreover, Han teaches primers 52, 11, 95 and probes 89 and 90a. Primer 95 overlaps SEQ ID NO: 1, i.e., the sequence CAGAAAGCGTCTAG is in common.

The examiner also notes that some of the claims for detecting the nucleic acid are not merely drawn to the specific probe oligonucleotides, the claims use open language, namely comprising to describe the probes, i.e. Claim 13.

6. Claims 14, 16-26, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996).

Kolykhalov et al. (herein referred to as Kolykhalov) teaches a highly conserved sequence at the 3' terminus of the HCV genome RNA. Kolykhalov teaches preparing HCV RNA from human serum (pg 3363, col 2)(limitations of Claim 21). Kolykhalov teaches using nested primer pairs corresponding to a region in the 5'NTR for RNA isolation (pg 3363, col 2). Furthermore, Kolykhalov teaches using primer pairs specific for the novel 98-base element at the 3' end of the HCV genome to analyze for the presence of novel sequences (pg 3364, col 1)(limitations of claim 16). PCR products were analyzed by electrophoresis on a polyacrylamide gel (limitations of Claim 14, 17, 18). Kolykhalov teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. The region is also found at the 3' termini of several independent HCV isolates which is highly conserved with between 98-100% sequence identity for the examined isolates. Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV replication and recovery of infectious HCV RNA from

cDNA, the apparent conservation of the 3' element may have important applications for HCV diagnosis and therapy"(pg 3370, col 2).

Kolykhalov does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply simply represent functional equivalents of primer 284 of Kolykhalvo a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Kolykhalov to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 3' UTR region to detect HCV, as taught by Kolykhalov. Since Kolykhalov provides an alignment of several isolates which show conserved regions between the isolates (Figure 3), the ordinary artisan would have been motivated to have designed primers which amplify the

98-nucleotide conserved region from the 3' UTR region. Specifically, the skilled artisan would have picked primers from the 5' and the 3' end of the 98-nucleotide conserved region of the 3' UTR which were conserved among the isolates, for example SEQ ID NO: 1. The ordinary artisan would have been motivated to amplify the 3' UTR region of HCV since Kolykhalov teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. Additionally, Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV replication and recovery of infectious HCV RNA from cDNA, the apparent conservation of the 3' element may have important applications for HCV diagnosis and therapy". Kolykhalov teaches an oligonucleotide 284 which overlaps SEQ ID NO: 1, 4-6 and contains SEQ ID NO: 2-3. Oligonucleotide 284 is considered a functional equivalent of SEQ ID NO: 1-6. Any primers found within the conserved region surrounding Oligonucleotide 284 which amplify the 98-nucleotide conserved region of the 3' UTR region and any probes within this 3' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The MPEP provides in 716.02(e) a requirement of Comparison With Closest Prior Art. The MPEP states, "An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular

limitations, will usually yield the closest single prior art reference." In re Merchant, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). Where the comparison is not identical with the reference disclosure, deviations therefrom should be explained, In re Finley, 174 F.2d 130, 81 USPQ 383 (CCPA 1949), and if not explained should be noted and evaluated, and if significant, explanation should be required. In re Armstrong, 280 F.2d 132, 126 USPQ 281 (CCPA 1960) (deviations from example were inconsequential). Applicant does not appear to have compared SEQ ID NO: 8-9 to the closest prior art, namely Kolykhalov (primer 284 and 285). The oligonucleotide 284 overlap SEQ ID NO: 9, namely 22/27 nucleotides of SEQ ID NO: 9. The oligonucleotides 285 of Kolykhalov overlaps the primer of SEQ ID NO: 8, namely 22/27 of SEQ ID NO: 9. However, these sequences are within the same region of conserved nucleotides as taught by Kolykhalov. The ordinary artisan would have been motivated to have targeted this region as specifically identified by Kolykhalov. Applicant does not appear to have compared SEQ ID NO: 8 and 9 to the closest prior art, namely Tanaka (primers in Table 2) and Kolykhalov (primer 285, 284).

As provided in the MPEP, "objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results." It is well settled that unexpected results must be established by factual evidence. The instant declaration does not provide any objective evidence to support the observations provided. For example, on page 7 of the Declaration, the declaration states that "very little or no gel bands were obtained", "somewhat more instense", "borad smears on the ethidium bromide gels, and not as sharp distinct bands

which are preferable". These descriptions have not been supported by factual evidence in the form of a gel, for example. The declaration has stated that primer 72R27 "gave very little or no gel bands", such that the primer pair of SEQ ID NO: 8 and 72R27 does not work. The delcaration states that the band obtained using 66R25 and 67R25 appeared as broad smeas and not as sharp distinct bands. The declaration states that SEQ ID NO: 8 and 9 yielded robust, clean bands. The declarations further states that "only the combination of forward primer 1F27 (SEQ ID NO: 8) and reverse primer 57R27 (SEQ ID NO: 9) successfully amplifies HCV nucleic acids with sufficient sensitivity and specificity for use, e.g., in clinical assay". It is noted that the declaration was not drawn to sensitivity or specificity, since the declaration was not drawn to detection of certain quantities of nucleic acids nor only HCV nucleic acids. The declaration illustrates that one primer pair did not work. The art teaches that Primer 7 and 11 were used (Tanaka, col 12). The primer 7 which was used and worked contains the same 5' end of the primer. Therefore, absent a comparison and explaination, it is unclear why the primers in the art work, while the primers in the declaration fail. Looking at the alingment of the primers which work and the primers which are asserted not to work, the primers which encompass, the greatest porition of primer 284 of Kolykhalov yeilds the best results, namely SE QID NO: 9. Therefore, there is no evidence that SEQ ID NO: 9 and the primer of 284 are not functional equivalents. The primers which are closest to the 3' end of the HCV region do not appear to have the same properties as those found in the region of 284.

Moreover, MPEP 716.02(d), provides that the unexpected Results must be Commensurate in Scope With Claimed Invention. Applicant has provided an analysis of SEQ ID NO: 8 and 9. Since the claims are drawn to oligonucleotides and primers consisting of SEQ ID NO: 8-9, the results are commensurate in scope with the nucleic acid sequences. However, this is not commensurate in scope with the claims since the Claims are drawn to SEQ ID NO: 1-14. The unexpected results for pairs of primers does not provide commensurate results for single primers. The declaration has used primer of SEQ ID NO: 9 in each of the analysis, therefore, the results may at most show that the primer pair including SEQ ID NO: 9 yields unobvious results, however this does not provide any evidence to SEQ ID NO: 9 as unexpected.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 51-53 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996) as applied to Claims 14, 16-26, 40-42 above, and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Kolykhalov does not specifically teach packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Kolykhalov with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Kolykhalov into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Kolykhalov's deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers included, into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 14, 16-26, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998).

Tanaka et al. (herein referred to as Tanaka) teaches the 3' UTR region of HCV. As seen in Table 2, numerous primers and a probe for this region are taught. Tanaka also teaches analysis of clinical samples (col 8). RNA was prepared from serum and

reverse transcription was carried out using specific primers (col. 8, lines 18-22)(limitations of Claim 16, 17, 21). The cDNA synthesized was mixed with primers, and the PCR product was detected upon agarose electrophoresis (col 11, lines 10-16)(limitations of Claim 18, 24). A southern blot was also used for conformation (limitations of Claim 19, 25). A probe R3 was used for detection (col 11).

Additionally, Encke et al. (herein referred to as Encke) teaches "recently, a highly conserved, 98 nucleotide long sequence at the very 3' end of the HCV genome which is the third region has been described and appears to play an important role in viral replication and possible infectivity (pg 118, col 1).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Tanaka and the teachings of Encke to obtain the claimed invention as a whole. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent functional equivalents of the probes and primers provided by Tanaka to amplify the disclosed 3' UTR of the HCV sequence. A biochemist of ordinary skill would attempt to obtain alternate compounds

with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference. Since Tanaka teaches the 3' UTR sequence and the 98 nucleotide conserved region, the skilled artisan would have designed primers within this 98 nucleotide region for the express benefit of detection of HCV. The skilled artisan would have been motivated to have chosen oligonucleotides from the 98-nucleotides since Tanaka teaches that "since the HCV gene is RNA, the viral RNA must be converted to DNA by a reverse transcription reaction prior to PCR. Consequently, the RT-PCR technique is used. Any primer which specifically hybridizes the "sequence 3'X" can be used, but those which are highly homologous to the "Sequence 3'X" and have length of about 20 residues are most suitably used" (col. 2, lines 48-55). Thus, any oligonucleotides from the 3' UTR region would have been obvious for reverse transcribing. Tanaka in essence is teaching that all of these oligonucleotides are functional equivalents.

Response to Arguments

The response traverses the rejection. The MPEP provides in 716.02(e) a requirement of Comparison With Closest Prior Art. The MPEP states, "An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." In re Merchant, 575

F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). Where the comparison is not identical with the reference disclosure, deviations therefrom should be explained, In re Finley, 174 F.2d 130, 81 USPQ 383 (CCPA 1949), and if not explained should be noted and evaluated, and if significant, explanation should be required. In re Armstrong, 280 F.2d 132, 126 USPQ 281 (CCPA 1960) (deviations from example were inconsequential). Tanaka teaches the full length 3'UTR region with specific probes and primers within the nucleic acid. Tanaka teaches that the 3'UTR sequence is highly conserved between clones and would be very useful for the detection of HCV. As seen in Table 2, SEQ ID NO: 8 overlaps each of primers 8, 9, 11, and 13 of Tanaka. Primer 13 provides the 5' end and primer 9 illustrates the 3' end. Further SEQ ID NO: 14 and 15 of the instant application overlaps each or R3, 14 and 15. Finally SEQ ID NO: 9 overlaps 14 10 and 7(12). Thus, guidance to these regions is provided. Applicant does not appear to have compared SEQ ID NO: 8-9 to the closest prior art, namely Tanaka (primers in Table 2).

As provided in the MPEP, "objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results." It is well settled that unexpected results must be established by factual evidence. The instant declaration does not provide any objective evidence to support the observations provided. For example, on page 7 of the Declaration, the declaration states that "very little or no gel bands were obtained", "somewhat more instense", "borad smears on the ethidium bromide gels, and not as sharp distinct bands which are preferable". These descriptions have not been supported by factual evidence

in the form of a gel, for example. The declaration has stated that primer 72R27 "gave very little or no gel bands", such that the primer pair of SEQ ID NO: 8 and 72R27 does not work. The delcaration states that the band obtained using 66R25 and 67R25 appeared as broad smeas and not as sharp distinct bands. The declaration states that SEQ ID NO: 8 and 9 yielded robust, clean bands. The declarations further states that "only the combination of forward primer 1F27 (SEQ ID NO: 8) and reverse primer 57R27 (SEQ ID NO: 9) successfully amplifies HCV nucleic acids with sufficient sensitivity and specificity for use, e.g., in clinical assay". It is noted that the declaration was not drawn to sensitivity or specificity, since the declaration was not drawn to detection of certain quantities of nucleic acids nor only HCV nucleic acids. The declaration illustrates that one primer pair did not work. The art teaches that Primer 7 and 11 were used (Tanaka, col 12). The primer 7 which was used and worked contains the same 5' end of the primer. Therefore, absent a comparison and explaination, it is unclear why the primers in the art work, while the primers in the declaration fail.

Moreover, MPEP 716.02(d), provides that the unexpected Results must be Commensurate in Scope With Claimed Invention. Applicant has provided an analysis of SEQ ID NO: 8 and 9. Since the claims are drawn to oligonucleotides and primers consisting of SEQ ID NO: 8-9, the results are commensurate in scope with the nucleic acid sequences. However, this is not commensurate in scope with the claims since the Claims are drawn to SEQ ID NO: 1-14. The unexpected results for pairs of primers does not provide commensurate results for single primers. The declaration has used primer of SEQ ID NO: 9 in each of the analysis, therefore, the results may at most show

that the primer pair including SEQ ID NO: 9 yields unobvious results, however this does not provide any evidence to SEQ ID NO: 9 as unexpected.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998) as applied to Claims 14, 16-26, 40-42 above, and further in view of Maertens et al (US Pat. 5,846,704, December 1998).

Neither Tanaka nor Encke specifically teach performing reverse transcriptase with random oligonucleotide primers.

However, Maertens et al teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68)(limitations of Claim 8). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68)(limitations of Claim 2). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the extraction method of Tanaka with the extraction method of Maertens to obtain the claimed invention as a whole. The ordinary artisan would have realized that RNA may be transcribed using either random primers, as taught by Maertens, or primers corresponding to specific

HCV RNA, as taught by Tanaka. Since the art teaches that RNA from HCV may be reverse transcribed using either random or specific primers, the ordinary artisan would have realized that they were equivalents and may have substituted random primers for primers corresponding to specific HCV regions.

Response to Arguments

The response traverses the rejection. The response asserts that Maertens does not teach or suggest any of the particular nucleic acid probes and primers of the invention. This argument has been reviewed but is not convincing because as argued above, Taqnaka or Encke both teach the 3' UTR region which is only 98 nucleotides in length, and primer design, absent secondary considerations is obvious. Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 7, 13, 33, 39, 47, 48, 58, 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claims 7, 13, 33, 39, 47, 48, 58, 59 are indefinite because the claims are directed to various probes for use when various combinations of primers are used. It is noted that the claims form which these claims depend have been amended to delete

recitation of SEQ ID NO: 3 (C143F26), 5 and 6. The probe of SEQ ID NO: 12 is to be used when said forward primer C131F25 or C143F26 is used. This primer lacks antecedent basis since claim 7, for example depends upon claim 1, from which SEQ ID NO: 3 has been deleted. Similarly, the other dependent claims lack antecedent basis for the same reasoning as above, i.e. lack of antecedent basis.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 22, 40-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 09/494,103. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the methods are directed to detecting the presence of 3'UTR HCV RNA in a biological sample by amplifying the reverse transcription products with SEQ ID NO: 9, in the instant application (which are identical to SEQ ID NO: 1 of 09/494,103) for detection.

Additionally, both applications are claiming SEQ ID NO: 9 of the instant application which is identical to SEQ ID NO: 1 of 09/494,103.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

12. In the specification Applicants have provided comparison results for the 5' NCR primers of the present invention and the Roche assay. Applicants have compared the primer pair SEQ ID NO: 1, 4 and SEQ ID NO: 2,7 with the Roche primers. It is noted that applicants have not provided the exact Roche primers which were compared. Applicants have shown that the instant primer pairs detect more positive results than the Roche primers. Since it is presumed that the positive results detected were samples which were infact infected, the instant primer pairs (SEQ ID NO: 1 and 4 and SEQ ID NO: 2 and 7), have unexpected results and are not obvious over the prior art. Applicants have compared their invention to the prior art and shown that improved results were found for the specific primer pairs. It is noted that applicants have not showed unexpected results for the individual primers, only the primer pairs.

13. Claims 1-6, 8, 9-12, 27-32, 34-38, 43-46, 49-50, 54-57, 60-61 have been limited to specific primer pairs, namely SEQ ID NO: 1 and 4 and SEQ ID NO: 2 and 7 which have been illustrated to have unexpected results.

Conclusion

14. Claims 1-6, 8-12, 27-32, 34-38, 43-46, 49-50, 54-57, 60-61 are **allowable over the art. Claims 7, 13-26, 33, 39-42, 47-48, 51-53, 58-59, 62-64 are rejected.**

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J Goldberg

Jeanine Enewold Goldberg
September 4, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600